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Ultrasonography for Thyroid Screening After Head and Neck Irradiation in Childhood Cancer Survivors

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We prospectively used ultrasonography to detect thyroid abnormalities in 96 long-term survivors of childhood cancer, who received head and neck radiation therapy at a median age of 8.9 years. The median time interval since irradiation was 10.8 years (range 5.6–22.8 years). Most survivors of leukemia received 24 Gy cranial irradiation for central nervous system prophylaxis; patients with solid tumors received between 20 and 66 Gy (median 37.5 Gy). The total evaluation included clinical history, physical examination, thyroid function tests, and thyroid ultrasonography; radionuclide scans were performed in patients whose abnormalities persisted on subsequent ultrasound exams. Clinical history and physical examination revealed thyroid abnormalities in 14 patients (15%), but ultrasound detected abnormalities in 42 patients (44%). These findings included inhomogeneity (n = 29), cysts (n = 15), and nodules (n = 22) and occurred in nearly half of patients treated with 15 Gy or more directly to the thyroid gland. Radionuclide scans confirmed the presence of thyroid nodules in 13 of 15 patients with ultrasonographic evidence of nodules. Six patients had thyroid neoplasia, including one case of papillary carcinoma. All patients with neoplasia had nodules demonstrated on ultrasonography. Our experience suggests that in childhood cancer survivors, ultrasonography is a sensitive, affordable, and noninvasive means of detecting subtle parenchymal abnormalities. We recommend thyroid ultrasonography for childhood cancer survivors who recieved head and neck irradiation. A baseline study should be obtained within 1 year of completion of therapy. The frequency of subsequent examinations should be based on the radiation dose and the patient's age at the time of irradiation.

Key words: thyroid ultrasonography, childhood cancer survivors, post-irradiation

INTRODUCTION

Thyroid dysfunction and an increased incidence of benign and malignant thyroid nodules can follow head and neck irradiation. Previous reports indicate that 40–90% of survivors of Hodgkin's disease, non-Hodgkin's lymphoma, brain tumors, and head and neck tumors develop overt or compensated hypothyroidism within 6 years of receiving radiotherapy doses of 30–60 Gy [1–5]. In 1985, a multi-center study found that 3% of 175 acute lymphoblastic leukemia (ALL) patients who received 24 Gy cranial radiation developed thyroid dysfunction 7 or more years after treatment [6]. More recently, Pasqualini et al. reported subtle circadian pattern primary hypothyroidism in patients treated for ALL. Primary thyroid failure was significantly more prevalent in patients treated with craniospinal irradiation (83%) versus cranial irradiation (25%) [7]. Although thyroid dysfunction is uncommon after cranial radiation, neoplasia has been reported after treatment with only 2 Gy or less [8–10]. Thus, long-term survivors of childhood ALL who received 18 to 24 Gy cranial radiation as central nervous system prophylaxis are at increased risk for developing thyroid neoplasia.

Thyroid nodules in cancer survivors are of particular concern because of the risk of malignancy. Although thyroid nodules are frequent sequelae of head and neck irradiation, treated patients are not consistently monitored. Physical examination is often unreliable. Fluctuations in serum thyroxine or triiodothyronine levels do not distinguish benign from malignant disease [4,9]. Radionuclide scans are invasive and expensive. The reliability of ultrasonography as an inexpensive, non-invasive screening tool and the correlation of ultrasound findings with clinical and biochemical abnormalities have not been established. We performed ultrasonography of the thyroid gland in 96 childhood cancer survivors treated with head and neck irradiation to determine its usefulness as a screening tool and correlate specific abnormalities with findings from physical examination, laboratory screening, and nuclear imaging.

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PATIENTS AND METHODS

Patients and Treatment

We prospectively studied 96 consecutive long-term survivors seen in the After Completion of Therapy Clinic at St. Jude Children's Research Hospital over a 14-month period. Eligible patients were those in complete remission at least 5 years after diagnosis who received irradiation near the thyroid gland. Of the 96 patients, 53 (55%) were boys, and 85 (89%) were white. The median age at diagnosis was 8.4 years (range 0.1–21.3 years). The median age at irradiation was 8.9 years (range 0.1–21.4 years). Patients were studied 5.6 to 22.8 years after diagnosis (median 10.6 years). The primary malignancies of these patients were Hodgkin's disease (n = 41), ALL (n = 28), non-Hodgkin's lymphoma (n = 15), rhabdomyosarcoma (n = 5), neuroblastoma (n = 4), nasopharyngeal carcinoma (n = 2), and Ewing sarcoma (n = 1).

Patients received mantle (n = 40), cranial (n = 25), head/neck (n = 19), craniospinal (n = 9), or mediastinal (n = 3) irradiation. Those diagnosed prior to 1978 were treated with orthovoltage radiation; patients diagnosed more recently received megavoltage radiation. A radiation oncologist (C.G.) retrospectively estimated the dose to the thyroid gland based on each patient's age at exposure, height, weight, body surface area, and estimated thyroid gland size. The patients then were assigned to one of three groups, according to the estimated thyroid radiation (Table I). For solid tumor patients, thyroid radiation doses ranged from 20 to 54 Gy (median 37.5 Gy). Of the 28 ALL survivors, 23 received 24 Gy to the cranium, which correlates with an estimated dose of 2 Gy to the thyroid; four received craniospinal radiation, and a single patient received cranial and craniospinal radiation for treatment of recurrent disease. Forty-six patients, the majority of whom were diagnosed with Hodgkin's disease and treated with mantle irradiation, received 31–66 Gy of thyroid irradiation (Table II). Twenty-five patients (primarily those with ALL) received <2 Gy radiation to the thyroid, and 25 patients received from 15 to 30 cGy. No patients received radiation doses to the thyroid between 2 and 15 Gy. Prior diagnosis of thyroid abnormalities did not preclude participation in this study. Five patients had undergone previous evaluation with ultrasonography; one of these had been evaluated with nuclear scintigraphy.

TABLE I. Estimated Radiation Dose to the Thyroid Gland

Thyroid radiation (Gy)	n	Age at diagnosis (years) Median	Age at diagnosis (years) Range	Follow-up (years) Median	Follow-up (years) Range
<2	25	4.5	1.5–17.6	10.6	6.7–15.3
15–30	25	8.6	1.1–18.7	8.4	5.8–17.8
31–66	46	11.2	0.1–21.3	11.2	5.6–22.8

TABLE II. Estimated Radiation Dose to the Thyroid Gland by Tumor Type

Diagnosis	n	Radiation to the thyroid gland <2 Gy	15–30 Gy	31–66 Gy
Hodgkin disease	41	0	10	31
ALL	28	23	4	1
Non-Hodgkin lymphoma	15	2	8	5
Solid tumors	12	0	3	9

Evaluation

The clinic staff assessed patients' thyroid function using a symptom checklist. In addition, patients were examined independently by two individuals (medical oncologists or oncology nurse practitioners) who described the size, position, symmetry, nodularity, and texture of the thyroid gland. Laboratory studies included a complete blood count, urinalysis, and thyroid function tests including thyroid-stimulating hormone (TSH), thyroxine (T4), and thyroxine-binding globulin concentrations, triiodothyronine resin uptake (T3), and free thyroxine index. We regarded plasma TSH concentrations between 5.1 and 10.0 uIU/ml as borderline. Concentrations above 10.0 uIU/ml were considered an indication for treatment with suppressive replacement therapy. Levels of anti-thyroid antibodies were obtained in the first 10 patients and in any patient with diffuse enlargement of the thyroid (n = 22).

Real-time thyroid ultrasonography using direct contact technique and a 5- or 7-mHz linear array transducer (Acuson, Mountain View, CA) was performed on all 96 patients, who were scanned in the recumbent position with neck hyperextension. Permanent copies were recorded on film. Thyroid scintigraphy with ^{99m}Tc-pertechnetate, ^{123}I, or ^{131}I (in a single case) was performed when the physical examination or ultrasound study revealed one or more thyroid nodules. All of the sonograms and scans were evaluated by a single radiologist (S.K.).

Analysis

Patients were determined to have thyroid nodules, cysts, or inhomogeneity based on results of physical examinations, biochemical evaluations, thyroid ultrasounds, and radionuclide scans. Biopsies obtained by fine-needle aspiration (FNA) were evaluated for the presence of thyroid neoplasia. We compared the occurrence of thyroid nodules, cysts, and inhomogeneity according to the estimated exposure of the thyroid to radiation. The relative risks of these abnormalities were calculated by comparing patients who received 15–66 Gy to those exposed to less than 2 Gy. Taylor series 95% confidence intervals were calculated for relative risk estimates [11]. Statistical analysis was performed using the SAS software package [12].

RESULTS

Clinical History

Eight of 96 patients (8%) reported clinical symptoms (primarily excessive fatigue and weight gain) that were suggestive of thyroid dysfunction. Only one of these had compensated hypothyroidism, with a borderline TSH of 9.2. Thyroid ultrasonograms for all of these patients were normal.

Physical Examination

There was a high correlation of findings on physical examination between the two independent examiners (89%). Abnormal thyroid glands were found in 13 of the 96 patients (14%) on physical examination. Of the 50 patients who received 30 Gy or less, 5 (10%) had diffusely enlarged thyroids. These patients were euthyroid. Ultrasound examination of the thyroid was abnormal in two of these five patients. In the first patient, who received 20 Gy thyroid irradiation, the gland was inhomogeneous. The second patient, whose thyroid was exposed to 22 Gy, had a single thyroid nodule.

Among the 46 patients whose thyroids were exposed to 31–66 Gy, eight were found to have thyroid abnormalities upon physical examination. Ultrasound findings also were abnormal in seven of these eight patients. Five patients with diffuse enlargement and/or nodule formation on physical exmination were found to have nodules on ultrasound. Two patients had small fibrotic thyroid glands on clinical exmination; thyroid ultrasonography demonstrated two cysts in one patient, and the other had a single nodule.

Biochemical Evaluation

Of the 96 patients, 11 (12%) had elevated TSH concentrations; none of these patients had a concurrent low T4 concentration. Ten of the 11 patients with biochemical abnormalities had marginally elevated TSH levels (range 5.0–10.0 uIU/ml) but normal ultrasound evaluations. However, the remaining patient, who was noncompliant with previously prescribed thyroid replacement therapy, had a TSH concentration of 51.4 uIU/ml. Ultrasound examination showed that this patient had multiple thyroid nodules. Anti-thyroid antibodies were studied in 22 patients, and all were negative.

Thyroid Ultrasound

Abnormal thyroid sonograms were obtained in 42 patients (44%) and are summarized according to estimated radiation dose (Table III). Nodules were detected in 22 (23%) of the 96 patients studied. Within these 42 patients, only eight patients had thyroid abnormalities detectable on ultrasound. Five patients had nodules and three had diffuse enlargement. Five patients had false-positive physical examinations with no abnormalities detected by ultrasonography. Patients exposed to greater than 31 Gy thyroid irradiation had significantly more thyroid nodules (31%) than those receiving less than 2 Gy (4%, $P = .017$). Sonography identified thyroid nodules in three ALL patients who had received craniospinal irradiation. Thyroid ultrasound confirmed palpable nodules in 13 of 15 patients treated with 31–66 Gy. In all 13 patients, these findings persisted on subsequent sonograms.

Radionuclide Scans

Radionuclide scans were performed in patients whose nodules, by palpation, were thought to be enlarging, noncystic, or were of a substantial size. Scans were performed in 15 of the 22 patients in whom ultrasound detected nodules greaer than 1.0 cm. In 13 patients, these scans confirmed the presence of nodules; the other two patients had normal scans.

Surgical Evaluation

Ten patients with "cold" nodules larger than 1.0 cm were referred for surgical consultation. These patients had received a median of 34.5 Gy (22–66 Gy) to the thyroid, and all ten patients were on levothyroxine. Four patients had palpable abnormalities, but the other six had nodules detectable only by ultrasonography and confirmed by radionuclide scan. Biopsies obtained by FNA were performed in these six patients. Four biopsies were normal, one was not evaluable, and one showed cellular atypia. The four patients with palpable abnormalities and the two with inconclusive biopsies went to surgery. Four of these patients received total lobectomies and two received subtotal lobectomies. Histologic evaluation documented four cases of adenoma, and one each of adenomatous goiter and papillary carcinoma. The details of these patients are summarized in Table IV.

Thyroid Abnormalities and Radiation Exposures

Nodules occurred in one (4%) of the patients who received <2 Gy thyroid irradiation; six (24%) of those exposed to 15–30 Gy and 15 (33%) of the patients that received 31–66 Gy had thyroid nodules (see Table V). The relative risk of nodules was 6.0 for the group whose thyroids were subjected to 15–31 Gy, compared to the patients who had doses <2 Gy (95% confidence interval, 1.05–34.21). The relative risk of nodules increased to 8.2 (95% confidence interval, 1.81–36.64) when patients who received 31–66 Gy thyroid irradiation were compared to those whose exposure was <2 Gy. Both relationships were statistically significant ($P = .05$). Although patients who experienced at least 15 Gy thyroid irradiation were at slightly increased risk for cysts or inhomogeneity (relative risk, 1.4 and 1.3, respectively), neither relationship was statistically significant.

TABLE III. Results of Thyroid Ultrasonography in 96 Radiated Patients

Radiation to thyroid (Gy)	Ultrasound results				
	Normal n (%)	Abnormal n (%), by radiation dosage[a]			
		Total	Nodule(s)	Cysts	Inhomogeneity
<2	18 (72)	7 (28)	1 (4)	3 (12)	6 (24)
15–30	12 (48)	13 (52)	6 (6)	0 (0)	10 (10)
31–66	23 (50)	23 (50)	15 (33)	12 (26)	13 (28)

[a]Many patients had more than one abnormality.

TABLE IV. Patients With Thyroid Neoplasia Following Head and Neck Irradiation

Patient No.	Primary diagnosis	Age at primary diagnosis (years)	Radiation dose (Gy/volume)	Latency (years)	Sonographic findings	Scan	Secondary diagnosis
1	Neuroblastoma	0.8	32/Mediastinum	16.8	Nodule	3-cm cold nodule	Adenomatous goiter
2	Neuroblastoma	2.0	22/right superior sympathetic ganglion	14.9	Inhomogeneity multiple cysts single nodule	Enlarging 1.5-cm nodule	Papillary carcinoma, follicular variant
3	Non-Hodgkin's lymphoma	4.3	32/mediastinum supraclavicular	11.8	Nodule	1-cm cold nodule	Follicular adenoma
4	Non-Hodgkin's lymphoma	10.3	66/neck	22.8	2 nodules	Multinodular gland, two cold nodules enlarging	Adenomatoid nodules with atypical features
5	Hodgkin's disease	12.7	40/mantle	15.3	Multiple nodules	Multiple nodules	Well-differentiated follicular adenoma
6	Hodgkin's disease	21.4	35/mantle	11.0	2 nodules	Cold nodule	Follicular adenoma

DISCUSSION

Ultrasonography detected thyroid abnormalities in 42 (44%) of 96 survivors of childhood cancer who were treated with head and neck irradiation, compared to the 14% with palpable lesions. Thyroid nodules were detected by ultrasonography in 22 (23%) of the 96 patients and were significantly more frequent in patients whose thyroid exposures to radiation reached at least 31 cGy. Radionuclide scans confirmed the ultrasonographic diagnosis of thyroid nodules in 13 of 15 patients.

Radiation increases the risk of thyroid neoplasia. External radiation in pediatric cancer patients may initiate carcinogenesis in surrounding organs through increased spontaneous mutation and DNA damage [13]. In addition, increased secretion of TSH resulting from impaired thyroid hormone secretion may contribute to radiation-induced carcinogenesis [14–16].

Many factors are implicated in the etiology of radiation-induced thyroid cancer in survivors of pediatric cancer. Identified risk factors include female gender, younger age at irradiation, and greater elapsed time since irradiation [17,18]. The incidence of thyroid neoplasia is dose dependent, but is increased even with exposures as small as 0.05 Gy [19,20]. This implies that leukemia survivors treated with 24 Gy cranial irradiation, who receive an estimated 7.5% of the total dose (1.8 Gy) to the thyroid, are at risk for radiation-induced thryoid cancer [21].

The prevalence of thyroid neoplasia in irradiated survivors of pediatric cancer is unknown. A 1991 epidemiological investigation of 9,170 patients who had survived childhood cancer at least 2 years reported a 53-fold increased risk of thyroid neoplasia. Doses less than 2 Gy were associated with a 13-fold increased risk. Furthermore, the risk of thyroid neoplasia did not decrease even after doses as high as 60 Gy [22]. In contrast, Maxon and colleagues found that most thyroid neoplasms subsequent to external irradiation developed after doses lower than 20 Gy. They hypothesized that radiation doses greater than 31 Gy would be more likely to render thyroid follicular cells atrophic, rather than neoplastic [23].

There are conflicting reports about the latency of radiation-induced thyroid malignancy. Some recent studies report thyroid neoplasia as soon as 1.5–6 years after radiotherapy [20]. In contrast, other lesions are more indolent and may be latent for more than 20 years [22,24]. DeGroot calculated that new nodules develop at a rate of about 2% annually, reaching a peak 15–25 years after an exposure of 2–5 Gy [25]. In view of the potentially indolent nature of thyroid neoplasia secondary to radiotherapy, the optimal method and frequency of screening has not yet been determined.

"Small parts" ultrasonography is the most sensitive imaging modality for anatomic assessment of the thyroid

TABLE V. Numbers of Patients and Relative Risks of Nodules According to Level of Thyroid Irradiation

	Thyroid radiation exposure					
	<2 Gy[a]		15–30 Gy		31–66 Gy	
Thyroid outcome	N	%	N	%	N	%
Nodules						
No	24	96	19	76	31	67
Yes	1	4	6	24	15	33
Total	25	100	25	100	46	100
Crude relative risk	1.0		6.0		8.2	
95% C.I.[b]			1.05–34.21		1.81–36.64	

[a]Reference group.
[b]Taylor series 95% confidence intervals.

gland. Recent reviews have demonstrated that its sensitivity for detecting thyroid parenchymal abnormalities far exceeds that of clinical examination or thyroid scintigraphy [26–33]. The normal thyroid gland typically shows homogeneous intermediate echogenicity. Echo abnormalities, the number of which may increase with age, occur in approximately 27% of the normal population and are more prevalent in women [34]. The high prevalence of inhomogeneity in our population (44%) may represent an acceleration of normal thyroid aging or may be induced by radiotherapy. Nodules are frequently found at autopsy in clinically normal thyroid glands [30–32,34], and the utility of ultrasound's detection of clinically occult lesions has not been determined [32,34,35]. Carcinoma has been detected even in lesions less than 4 mm in diameter [29,35]. Thus, in those patients at risk for developing thyroid carcinoma, early detection of small lesions may decrease patient morbidity and mortality. Attempts at delineating ultrasound characteristics of benign versus malignant lesions [26,31,36,37] have been unsuccessful, largely due to the overlapping characteristics. Further, these efforts have limited usefulness in high-risk patients like those presented here. However, findings suggestive of benignancy may support a period of close follow-up for patients in whom biopsy or resection need be avoided. The ultrasonographic character of thyroid nodules correlated poorly with nodule activity as determined by scintigraphy. Neither ultrasonography nor nuclear scintigraphy alone or in combination can accurately assess the relative malignancy of thyroid lesions [26,29,33,35,38].

Most imaging modalities are confounded by lobar atrophy and nodule formation in the thyroid following radiotherapy. In contrast, progressive sonographic changes have been demonstrated in the thyroids of patients previously treated with radiation therapy to the head and neck [30,38,39]. Not only is ultrasonography readily accessible, non-invasive, and sensitive, but its lack of ionizing radiation is a particular advantage when evaluating children and young adults [26]. Thyroid ultrasonography also is cost-effective, costing about half that of a ^{99m}Tc thyroid scan.

Ultrasound has greatly facilitated fine-needle aspiration (FNA) biopsy of thyroid lesions, particularly those which are non-palpable. However, FNA biopsy is not always diagnostic, and false-negative cytology results have been reported for samples obtained from predominantly cystic lesions (previously thought to represent benign nodules). These inaccuracies presumably are due to inadequate sampling or sampling error [26,29–33,35].

We calculated a conservative relative risk estimate using the children who received <2 Gy as our reference population. Survivors in our study exhibited a dose-response relationship between radiation exposure to the thyroid and risk of nodule formation. Survivors who received 15–30 Gy were 6.0 times and those who received 31–66 Gy were 8.2 times more likely to develop nodules 10.8 years after exposure than patients receiving <2 Gy, a relationship that was statistically significant at the .05 level.

Only one patient had papillary carcinoma. This low incidence of malignancy may reflect a median follow-up of less than 12 years. However, even this incidence of thyroid cancer far exceeds that in the general population of 49 per million per year [40]. In addition, adenomas must be carefully monitored. These lesions may slowly increase in size to cause pressure symptoms in the neck, become painful secondary to intralesional hemorrhage, or synthesize T3 or T4 and cause hyperthyroidism [41].

No single historical factor, physical finding, or clinical laboratory result is pathognomonic of thyroid neoplasia. Biochemical screening is of little help, since total serum T4 levels may not differ between benign and malignant disease. Physical examination is often inconclusive with palpable abnormalities being relatively large. This study demonstrates that ultrasonography is exquisitely sensitive in identifying abnormal thyroid glands. Early detection of indolent lesions should decrease morbidity and mortality related to secondary thyroid malignancies in patients

treated with head and neck radiation. Our study suggests that because ultrasound detects subtle architectural changes in the thyroid gland, it may be useful in screening patients at risk for the development of thyroid neoplasia. We conclude that periodic ultrasound evaluation is a useful screening study for pediatric cancer survivors who received 15 Gy or more directly to the thyroid gland. A baseline ultrasound evaluation should be performed within 1 year of the completion of therapy, and periodic evaluations every 2–3 years may be helpful in screening this high-risk population for nodular changes.

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